·Clinical Research·

Risk factors for clinically significant macular edema in a multi-ethnics population with type 2 diabetes

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Abstract

• AIM: To determine the risk factors of clinically significant macular edema (CSME) in patients with non-proliferative diabetic retinopathy (NPDR) in a multi-ethnics Malaysian population.

• METHODS: We performed a case control study in which 150 patients with bilateral NPDR and CSME in either eye were compared to 150 patients with bilateral NPDR and no CSME in both eyes. CSME and NPDR were graded according to Early Treatment of Diabetic Retinopathy Study criteria. Student's *t* test, odds ratio and multiple logistic regression analysis were performed to analyze the duration of diabetes, body mass index (BMI), blood pressure (BP), total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), fasting blood glucose (FBG), HbA1c, full blood count, serum creatinine and proteinuria between the two groups.

• RESULTS: Both groups were matched in terms of age, gender and ethnicity. Duration of diabetes, total serum cholesterol, serum LDL, FBG, HbA1c and serum creatinine were significantly higher in the CSME group ($P<0.05$). The hemoglobin, packed cell volume were significantly lower in the CSME group ($P<0.05$). There was no significant difference for serum HDL, TG, BMI, systolic and diastolic BP. Multiple logistic regression analysis showed that total serum cholesterol and HbA1c had significantly high odds of developing CSME.

• CONCLUSION: HbA1c and total cholesterol are the two most important risk factors associated with CSME in patients with NPDR.

• KEYWORDS: risk factors; clinically significant macular edema; diabetes
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INTRODUCTION

Diabetic macular edema is the major cause of central vision loss among patients with diabetic retinopathy. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) revealed that after 15 years of known diabetes, the prevalence of diabetic macular edema was approximately 20% in patients with type 1 diabetes mellitus (DM), 25% in patients with type 2 diabetes mellitus (DM) who were on insulin, and 14% in patients with type 2 DM who were not on insulin [1-3]. The pathophysiology of the macula edema is multifactorial and not fully understood. Diabetes accelerated neurotoxicity has been postulated to damage the ganglion cell and inner plexiform layer. At the same time, impairment of vascular autoregulation accompanied by capillary pericyte loss, thickening of capillary basement membranes, and delayed leukocyte migration have been found to be associated with the formation of diabetic macular edema.

Systemic factors such as fluid retention and hypertension has been implicated in the development of macula edema, too [4,5]. Many studies had been done to identify the risk factors or associations of diabetic macular edema. However, the associations varied from one study to another. The variation in the result may be due among other things to epidemiological differences. Duration of diabetes, glycaemic control, lipid profiles, hypertension and nephropathy were the few main risk factors found to be associated with increased risk of retinopathy and macular edema [6-12]. In Malaysia, the third National Health and Morbidity Survey (NHMS III) in 2006 reported a prevalence of diabetes of 14.9% in subjects above 30 years as compared to 6.3% in the First National Health and Morbidity Survey (NHMS I, 1986) and 8.3% in the Second National Health and Morbidity Survey (NHMS II, 1996). These numbers are alarming as it showed that the prevalence had increased by 80% over a decade, representing an average of 8% rise per year [13]. A study done in University Malaya Medical Center showed a high prevalence rate of diabetic maculopathy of 26.7% while the overall diabetic retinopathy prevalence rate was 51.6%. This means that about half of all patients with diabetic retinopathy may presents with maculopathy [14]. In view of the increasing numbers of diabetic maculopathy in Malaysia, and because diabetic maculopathy is a condition

that is difficult to treat, we feel a need to identify the risk factors involved, so as to be able to prevent it or help in the management. The aim of this study was to evaluate the systemic risk factors of clinically significant macular edema (CSME) in patients with non-proliferative diabetic retinopathy (NPDR) in a state government hospital in Malaysia.

SUBJECTS AND METHODS

Subjects It was a case control study involving diabetic patients who attended ophthalmology clinic in Malacca Hospital, one of the state hospitals under the preview of the Ministry of Health in Malaysia. The classification of diabetic retinopathy and macular edema were referred to as in the ETDRS study [15]. CSME was defined as presence of either one of the following: 1) Any retinal thickening at or within 500 microns of the centre of the macula; 2) Hard exudates within 500 microns of the centre of macula with adjacent retinal thickening; 3) Retinal thickening of one disc diameter or more, any part of which is within one disc diameter from the centre of macula.

Two groups of patients were recruited. Group A were subjects with both eyes NPDR and presence of CSME in either eye. Group B were control subjects with both eyes NPDR and absence of CSME in both eyes. A total of 150 patients were recruited in each group. The clinical fundus findings were confirmed by 2 ophthalmologists using 78 Diopter lens and if only there was agreement between them with regards to the diagnosis of NPDR and CSME, were the patients included.

Subjects who fulfilled the inclusion and exclusion criteria were identified. Informed consent was taken. The following information was obtained: 1) Demographic characteristics include age, gender and ethnicity; 2) Duration of diabetes; 3) Presence of other co-morbidities include hypertension, ischaemic heart disease, nephropathy, neuropathy; 4) Current treatment; 5) History of smoking; 6) On aspirin or antilipid treatment; 7) Does regular exercise or not (regular exercise being defined as exercise lasting at least 15 minutes each session, at least 3 times a week).

Systolic and diastolic blood pressures (BP) were measured one hour apart and average reading was recorded. Height and weight of the subject were measured and body mass index (BMI) calculated. Refractive assessment was performed by one optometrist and best corrected visual acuity (BCVA) was recorded.

The following blood tests were taken: 1) Full blood counts include haemoglobin, hematocrit, total white and platelet count; 2) Serum urea and creatinine; 3) Fasting serum lipid and its components include total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides (TG); 4) Fasting blood glucose (FBG); 5) HbA1c; 6) Liver function tests include serum albumin. All the laboratory tests were performed with autoanalyser (Roche Modular P-800, Germany). LDL was derived by using Friedewald's formula.

Table 1 Demographic data of recruited patients included age, gender and ethnicity

Demographic data	CSME group (n=150)	Control group (n=150)	P
Age (a, $\bar{x} \pm s$)	58.20±7.07	60.04±7.54	0.211
Gender, n (%)			0.317
Male	63(42)	81(54)	
Female	87(58)	69(46)	
Ethnicity, n(%)			0.265
Malay	93(62)	81(54)	
Chinese	33(22)	54(36)	
Indian	24(16)	15(10)	

Statistical Analysis The data was analyzed with SPSS software version 16.0. Independent Student's t test (two-tailed) was used to compare means of quantitative data between the two groups. Chi-square test was used to compare qualitative data between two groups. Odds ratio was calculated to see the magnitude of associations. Multiple logistic regression was used to analyze the association between all the relevant variables by eliminating the possible confounding factors. Pearson's correlation test was performed to examine various correlations between two groups. $P \leqslant 0.05$ was considered statistically significant.

RESULTS

Demographic Characteristics One hundred and fifty subjects from group A and 150 subjects from group B were recruited in the study. There were 63 males (42%) and 87 females (58%) with a mean age of (58.20±7.07) years in group A. There were 81 males (54%) and 69 females (46%) with a mean age of (60.04±7.54) years in group B. There was no significant difference in gender and age between the two groups (P>0.05). Both groups were matched in terms of age, gender and ethnicity distribution. Table 1 showed the summary of the demographic features with significant values. There was no significant difference between the two groups in terms of other co-morbidities or treatment options (P>0.05). There was also no difference between two groups in terms of aspirin treatment, antilipid treatment or smoking status. However, group B had significantly more subjects who practiced regular exercises. The details were illustrated in Table 2. The summary of the comparison between both groups was illustrated in Table 3.

The risk factors which showed high significance level of P= 0.001 or more include duration of diabetes, serum cholesterol, FBG, HbA1c and serum albumin. Other risk factors which also showed significant difference include haemoglobin, packed cell volume, urea, creatinine and LDL. There was no significant difference between both groups for the BMI, systolic and diastolic BP, HDL, triglycerides, total white counts and platelet counts.

Table 2 Medication and life style included smoking and exercise in studied patients *n*(%)

	Group A	Group B	*P*
Aspirin			>0.05
No	123 (82)	120 (80)	
Yes	27 (18)	30 (20)	
Antilipid Rx			>0.05
No	96 (64)	96 (64)	
Yes	54 (36)	54 (36)	
Smoking			0.30
No	129 (86)	114 (76)	
Yes	21(14)	36 (24)	
Exercise			0.02
No	47 (94)	38 (76)	
Yes	3 (6)	12 (24)	

Table 3 Systemic factors in studied groups

	CSME group	Non-CSME group	*P*
Duration of DM (a)	12.72±6.59	8.57±5.66	0.001
BMI (kg/m^2)	24.80±4.71	25.66±4.13	0.335
Diastolic BP(mmHg)	87.58±10.65	86.02±10.36	0.460
Systolic BP(mmHg)	148.04±29.52	140.56±18.82	0.134
Hb (g/dL)	122.86±21.994	133.94±15.178	0.004
PCV (%)	35.636±7.613	39.076±4.032	0.006
Platelet (x10^9/L)	249.38±68.551	254.92±62.842	0.675
TWBC (x10^9/L)	8.586±1.892	8.392±2.235	0.641
Urea (mmol/L)	6.530±3.171	5.078±1.747	0.006
Creatinine (μmol/L)	125.00±86.02	90.94±36.76	0.012
Total Cholesterol (mmol/L)	6.243±1.910	4.896±1.013	<0.001
HDL (mmol/L)	1.443±0.321	1.352±0.264	0.125
LDL (mmol/L)	3.647±1.606	2.718±1.038	0.001
TG (mmol/L)	2.383±1.453	1.894±1.361	0.085
FBS (mmol/L)	9.566±4.069	6.712±1.995	<0.001
HbA1c (%)	10.358±2.245	7.854±1.263	<0.001

PCV: Packed cell volume; Hb: Haemoglobin; FBS: Fasting blood sugar; TG: Triglyceride; LDL: Low density lipoprotein; HDL: High density lipoprotein; DM: Diabetes mellitus; BMI: Body mass index.

Duration of diabetes among the CSME group (12.72±5.66) years was significantly higher than the non-CSME group (8.57±5.66) years with $P = 0.001$.

Serum cholesterol in the CSME group (6.243±1.910)mmol/L was significantly higher compared to the non-CSME group (4.896 ±1.013)mmol/L. Serum LDL in the CSME group (3.647±1.606)mmol/L was also significantly higher than the non-CSME group (2.718±1.038)mmol/L.

FBG in the CSME group (9.566±4.069)mmol/L was significantly higher (P <0.001) compared to the non-CSME group (6.712 ±1.995)mmol/L. Glycosylated haemoglobin, HbA1c, was also significantly higher (P<0.001) in the CSME group (10.358 ±2.245)mmol/L as compared to the non-CSME group (7.854±1.263)mmol/L.

The haemoglobin level was lower (P=0.004) in the CSME group (122.86±21.994)g/dL as compared to the non-CSME group (133.94 ±15.178)g/dL. The packed cell volume (hematocrit) was also lower in the CSME group as compared to the non-CSME group (35.63 ±7.61% *vs* 39.07 ±4.03% [Normal range 35%-50% minimum in female and maximum in male] P=0.006).

Table 4 Hematological factors odds ratio in recruited patients

Factors	OR	95%CI(lower level/ higher level)
Duration of DM >5 years	2.79	1.11/7.01
Total cholesterol >5.1mmol/L	3.43	1.46/8.06
HDL <1.1mmol/L	0.84	0.26/2.70
LDL >2.6mmol/L	2.36	0.98/5.68
TG > 1.7mmol/L	1.50	0.68/3.29
FBS ⩾6.1mmol/L	4.83	1.82/12.79
HbA1c ⩾8%	11.97	4.29/33.40
Hb<120g/dL	3.80	1.48/9.75
PCV<35%	3.04	1.21/7.60

PCV: Packed cell volume; Hb: Haemoglobin; FBS: Fasting blood sugar; TG: Triglyceride; LDL: Low density lipoprotein; HDL: High density lipoprotein; DM: Diabetes mellitus.

The urea and creatinine level were significantly higher in the CSME group. The urea level in the CSME and non-CSME group were (6.530±3.171)mmol/L and (5.078±1.747)mmol/L whereas the creatinine level were (125.00±86.02)mmol/L and (90.94±36.76)mmol/L respectively. The albumin level in the CSME and the non-CSME group were(40.24±4.47)mmol/L and (44.12±2.32)mmol/L respectively.

Odds Ratio of Risk Factors Associated with CSME

Odds ratio, predicts the magnitudes of association between exposure and outcome. For the risk factors which showed significant difference between two groups, the odds ratios were calculated (Table 4). The confidence interval indicated the higher and lower level of the risk. From the data in Table 4, it was noted that for HbA1c>8% and FBG ⩾6.1mmol/L, the OR of developing CSME were 11.97 and 4.83 respectively. The wide confidence interval in HbA1c could be due to the relatively small sample size. For lipid profiles, the OR of having CSME was 3.43 times higher in subjects with cholesterol >5.1mmol/L.

Multiple Logistic Regression for the Risk Factors

Multiple logistic regression analysis was performed in order to eliminate the possible confounding factors in the study. Age, gender, duration of diabetes, aspirin treatment, antilipid treatment, smoking, exercise, diastolic BP, systolic BP, BMI, haemoglobin, PCV, platelet count, total white count, urea, creatinine, total cholesterol, HDL, LDL, TG, FBS, HbA1c and albumin were included in the regression analysis.

The results of risk factors with significant odds ratio were shown in Table 5. Of all the variables, total cholesterol and HbA1c showed a significantly high odds ratio of 3.504 and 2.955 respectively.

This means that for each unit increase in total cholesterol, the OR of having CSME was 3.5 times higher. Similarly, for each unit increase in HbA1c, the odds of having CSME was 3 times higher.

Table 5 Risk factors with significant odds ratio

	R	*P*	Odds ratio	95% CI for OR	
				Lower	Upper
Exercise	-3.029	0.015	0.048	0.004	0.561
Systolic blood pressure	0.042	0.024	1.043	1.006	1.083
PCV	-0.207	0.045	0.813	0.665	0.996
Total Cholesterol	1.254	0.011	3.504	1.325	9.263
HbA1c	1.084	0.000	2.955	1.734	5.038

PCV: Packed cell volume.

Exercise, PCV and albumin showed odds ratio of less than one. This means that subjects with regular exercises have 21 times higher odds of not having CSME. Each unit increase in PCV and albumin are associated with 1.23 and 1.75 times higher odds of not having CSME respectively. However, these data ought to be interpreted with care. When the higher level of the CI is very close to 1, the result may be due to chance, selection bias, or due to small sample size. Systolic BP had a low odds ratio of 1.043 which may not be significant due to same reason.

DISCUSSION

This case control study was carried out to evaluate the risk factors for CSME. There were limited studies in the literature that were designed specifically for diabetic macular edema. Most of the studies were about diabetic retinopathy in general. We realised that the stages of diabetic retinopathy may have an influence to the outcome of each risk factor. To minimize the effect of confounding factors related to the stages of diabetic retinopathy, this study was designed so that only subjects with NPDR in both eyes were selected. However, the severity of NPDR was not further classified. If we had done it so, the evaluation of the results will be affected due to the small sample size in the subgroups. This is the limitation of this study.

There has been increasing interest in the link between serum lipids and maculopathy in view of the evolving medical treatment. However, the results from the studies on association between lipid profiles with diabetic retinopathy and macular oedema are not consistent [7-12]. Previous prospective studies showed a stronger evidence for role of serum lipids in exudative maculopathy include the Early Treatment Diabetic Retinopathy Study (ETDRS) and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) cohort. In the ETDRS, it was reported that higher baseline total and LDL cholesterol levels increased the risk of retinal exudation by two-fold [8]. Those patients with higher baseline total cholesterol, LDL cholesterol or triglycerides had a greater risk of developing maculopathy during the course of the study. Elevated serum cholesterol at baseline also increased the risk of visual loss by 50% compared to lower serum cholesterol levels. There was also a significant trend for increasing severity of diabetic retinopathy and of retinal hard exudate with increasing cholesterol in insulin-using persons [9]. However, in multiple logistic regression analyses, cholesterol was a significant risk factor for retinal hard exudates but was not a significant descriptor of severity of retinopathy. In a later report on the cohort of the younger-onset group in the WESDR population, the relationships of total cholesterol and HDL to diabetic retinal lesions were predictive in univariate analysis but the relationships were no longer significant in multivariate analysis [10]. In a prospective study on the DCCT cohort on type I diabetic subjects, both total-to-HDL cholesterol ratio and LDL predicted the development of CSME [15]. There were other smaller studies which supported the associations between lipids and diabetic macular edema. Few studies found positive associations between total cholesterol and LDL with diabetic macular edema [6,12,16]. However, in a study to compare 3 groups of patients with chronic diabetic macular edema and plaque-like hard exudates, diabetic macular edema and DM patients but without retinopathy, there was no correlation between serum lipid levels and macular edema severity [11]. In our study, total cholesterol and LDL level was found to be significantly higher in the subjects with CSME in univariate analysis. However, only total cholesterol was significant in multivariate regression analysis. This finding is consistent with most of the previous studies. The endothelium is primarily involved in the regulation of adhesion and aggregation of leukocytes and platelet. It is largely influenced by nitric oxide (NO), which is synthesized by endothelial NO synthase. Elevated lipid levels was postulated to cause endothelial dysfunction through a series of inflammatory response with release of tissue growth factors which later leads to biological changes in the vessel walls, LDL oxidation and quenching of nitric oxide. Endothelial dysfunction in hypercholesterolemic patients was hypothesized to be related to reduce bioavailability of NO [17]. The end result of the endothelial dysfunction is the breakdown of blood retinal barrier, leading to exudation, retinopathy and macular edema. The role of NO synthase was further supported by a study which suggested that defective endothelial synthase gene may contribute to macular edema [18]. Apart from that, elevated LDL and

triglycerides in type 1 diabetes patients were found to be associated with higher levels of fluorescent advanced glycation end products, which were thought to be involved in the pathogenesis of diabetes complications [19]. Hyperglycemia is another strong risk factor for diabetic retinopathy and diabetic macular edema. HbA1c had been shown to be a significant risk factors for diabetic macular edema in many previous studies [11,12,16,20,21]. Another issue is the association between HbA1c and lipid profiles which had been evaluated in few studies. It was showed that both HbA1c and FBS had direct correlations with cholesterol, TG and LDL and inverse correlation with HDL, the magnitude of correlation being higher for HbA1c [22]. HbA1c may predict the extent of dyslipidemia besides its primary role in monitoring glycemic control [23]. Therefore, the confounding effect of hyperglycemia on lipids needs to be considered when interpreting the relationship between diabetic retinopathy end points with lipid profiles. Most of the previous studies on lipids and diabetic macular oedema did not control for HbA1c. Thus, it was unclear to what extent the observed relationships were confounded by the degree of hyperglycemia. In this study, multiple logistic regression was performed to address this issue. In univariate analysis, high total cholesterol, LDL, HbA1c, FBG, urea and creatinine, longer duration of diabetes, as well as low haemoglobin, packed cell volumes, and albumin were found to be risk factors for developing CSME. Nevertheless, after performing multivariate analysis which took into consideration of the confounding influence of multiple variables, only total cholesterol and HbA1c had a significantly high odds ratio of developing CSME.

Duration of diabetes in this study was found to be significantly higher in the CSME group. However, the relationship was no longer significant in multivariate analysis. Few previous studies also demonstrated duration of diabetes as one of the risk factor for diabetic macular edema [6,11,12]. The presence of diabetic maculopathy was found to be associated with diabetes duration in either type of diabetes [6]. The importance of diabetes duration was also demonstrated by the Wisconsin Epidemiologic Study of Retinopathy data which showed an increased prevalence of diabetic maculopathy of 28% in patients whose age at the time of diagnosis was 30 years or older and whose diabetes duration was 20 years or longer [24].

Anemia and low hematocrit have been found to be associated with microvascular complications including diabetic macular edema. In this study, the CSME group was found to have lower hemoglobin and hematocrit level. Anemia is a common consequence in patients with diabetic nephropathy due to reduced erythropoietin production. Anemia may lead to progression of diabetic retinopathy by aggravating hypoxia in the retina, which then results in production of growth factors such as vascular endothelial growth factor [25,26]. However, the magnitude of anemia where changes may occur remain uncertain. In this study, the difference was statistically significant even though the result of both groups were within normal limits. Similarly for serum albumin, the result was significantly lower in the CSME group even though both groups were within normal limits. Hypoalbuminemia, which may be secondary to renal loss of albumin, has been postulated to be one of factors involved in the formation of macular edema [25]. Serum urea and creatinine level, which reflects the renal function, were significantly higher in the CSME group. All these findings were consistent with the previous studies which has identified nephropathy as one of the association for macular edema [6,17,25,26]. However, the relationship was no longer significant after multivariate regression analysis. In conclusion, high cholesterol and high HbA1c levels were the two most important risk factors that lead to the development of CSME in this study. This result was consistent with most previous studies underlining the need for better glycaemic and lipid control in the prevention of diabetic macular edema. The data from this study lends additional support to current treatment guidelines in Malaysia. We advocate strict glycemic and lipid control among diabetic patients especially those who are on the way to develop maculopathy.

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